REMARKS

Claims 1, 3, 6-7 and 15 are pending after entry of the amendments set forth herein. Claims 2, 4-5, and 8-14 have canceled without prejudice. Claims 1, 3 and 6-7 have been amended for clarification. Claim 15 is added. Support for these amendments is found at paragraph 18 of the specification. Therefore, no new matter is added. Reconsideration is requested.

OBJECTIONS TO THE CLAIMS

Claim 1 is objected to because the claim includes subject matter of the non-elected inventions, namely the detection of the mutations other than K8 R340X and methods which assay for a mutation in a protein.

With respect to detection of mutations other than K8 R340X as in Claim 1, the Applicants maintain that as the Office has stated that claim 1 has only been examined to the extent that the claim reads on the elected invention of detecting a predisposition to liver disease by assaying for a nucleic acid mutation resulting in the K8 R340X alteration, this claim has not been further limited in view of the previous species election, as the claim shall be restricted to this species if no generic claim is finally held to be allowable.

REJECTIONS UNDER §112, ¶2

Claims 3, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The present claims have been amended to clarify the intended subject matter. In view of the amendments, withdrawal of the rejection is requested.

REJECTIONS UNDER §112, ¶1

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph. Applicants submit that the amendments provided herein, clarify the intended subject matter of the invention, and answer the rejections made for a lack of written description.

With respect to enablement, Applicants respectfully submit that Claim 1 meets the requirements of 35 U.S.C. 112, first paragraph.

Applicants have previously submitted data from the present inventors regarding the importance of keratin 8 variants in acute liver failure and the importance of some K8 variants in African Americans with liver disease and in African American in general. A Declaration from the inventor is attached herewith providing this information in declaratory form.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

The instant specification teaches multiple mutations, both in keratin K8 and in K18, that are associated with liver disease, as shown in Tables 3 and 4, which mutations cover a number of different residues in these proteins. It is noted that many of these mutations have an underlying molecular logic, in that there is a destabilization of the protein, providing for a logical nexus between genetic defect and disease. As cited in Ku, et al. (*Keratin Mutations Predispose to Cryptogenic and and Noncryptogenic Liver Disease*; Gastroenterology, 2002, cited in IDS), there is an "extensive body of transgenic animal data showing that keratins play an essential role in protecting hepatocytes from mechanical and nonmechanical stresses". For example, Table 6 shows the molecular consequences of keratin mutations:

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1 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2 *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Table 6. Molecular Consequences of Keratin mutations

Mutations		Potential effects
K8	R340H	Destabilization
	G433S	Altering keratin phosphorylation
	R453C	Formation of a disulfide bond
	1-465(I) RDT(468)	Destabilization
K18	Δ 64-71(TGIAGGLA)	Destabilization
	E275G	Destabilization
	Q284R	Destabilization
	T294M	Interruption of ionic interaction
	T296I	Interruption of ionic interaction

The significant number of patients described in the present application with K8/K18 mutations provide several insights into keratin-associated liver diseases. For example, K8 Y53H, K8 G61C, and most prominently K8 R340H are shown to be mutation hot spots.

Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

"[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art, which routinely performs such long experiments.[5]

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3 See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
4 *In re Wands* 8 USPQ 2d at 1404
5 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

The claimed methods relate to the use of the many different polymorphisms for keratin K8 and K18 that are provided in the application. The sequence of polynucleotides is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on different samples. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay to determine the active variants, no undue experimentation is necessary.

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7] As discussed above, numerous working examples have been provided.

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with the equivalent of a doctoral degree in molecular biology techniques, although Applicants believe that a much lower skill level would be sufficient to perform the claimed methods. Furthermore, such technicians are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

There may be some non-functional variants within the genus defined by the claims. However, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

"To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims

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6 In re Borkowski, 164 USPQ at 645.
7 *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).
8 *In re Angstadt*, 190 USPQ at 218.

would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

In sum, the amount of experimentation required to practice the methods of the invention would not be undue because a) a working example has been provided, b) guidance is given on how to test the sequences has been provided, and c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the sequences.

The Office Action has stated that "it is well-recognized in the art that associations between polymorphisms and phenotypic traits are often irreproducible". Applicants submit that the present invention is based not only on association studies, but on supporting animal models. Further, the use of association studies is well-supported in guiding human health decisions. For example, the odds ratio for liver failure associated with the genetic markers of the present invention is higher than the odds ratio for the well-known association of smoking and heart disease.

Applicants submit that the recent Board decision, Appeal 2009-0938, Ex parte Xu et al. (copy attached) is relevant to the facts of the present application.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. In view of the above amendments and remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-605.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: August 28, 2009

By: _____
Pamela J. Sherwood, Ph.D.
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Enclosure(s): Declaration under 37 C.F.R. §1.132 (executed by Bishr Omary)

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JIANFENG XU, DEBORAH MEYERS, SIGUN ZHENG, PATRICK C. WALSH, WILLIAM B. ISAACS, EUGENE BLEECKER, and DAVID HERRINGTON

Appeal 2009-0938
Application 10/426,262
Technology Center 1600

Decided: March 27, 2009[1]

Before DONALD E. ADAMS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The two-month time period for filing an appeal or commencing a civil action, as provided for in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is a decision on appeal from the Examiner's final rejection of claims 1 and 5-8. Jurisdiction for this appeal is under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

"Intense genetic study of familial prostate cancer has resulted in the identification of numerous putative prostate cancer susceptibility loci and several candidate genes, along with a realization of the extensive genetic and etiologic heterogeneity that characterizes this disease" (Spec. ¶8). The Specification describes several mutations in the MSR1 (macrophage scavenger receptor) gene associated with prostate cancer risk (*id.* at ¶¶8, 10).

Claims 1 and 5-8 are pending and stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the claims contain subject matter not "described in the specification in such a way as to enable one skilled in the art . . . to use the [claimed] invention" (Ans. 4-5). Claim 1 is the only independent claim on appeal. Claims 5-8 depend on claim 1 and incorporate all its limitations. Claim 1 reads as follows:

1. A method of screening a subject for increased risk of prostate cancer, comprising:

detecting the presence or absence of an MSR1 mutation in said subject; and then

determining that said subject is at increased risk of prostate cancer due to the presence or absence of said MSR1 mutation;

said MSR1 mutation selected from the group consisting of the R293X mutation and the DF174Y[2] mutation.

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[2] The original claims refer to the mutation as "DF174Y", but the Specification refers to "D174Y" (Spec. ¶60) as does the Appeal Brief (see p. 3). We use the term "D174Y" throughout this opinion.

ISSUE ON APPEAL

Did the Examiner establish a reasonable basis to question the enablement for the full scope of the claimed method for screening a subject for increased risk of prostate cancer?

PRINCIPLES OF LAW

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d at 1562.

> It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility. See, e.g., *Blicke*, 241 F.2d at 720. But the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." *Nelson*, 626 F.2d at 856. (emphasis added). In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior. See *Cross*, 753 F.2d at 1050.

Fujikawa v. Wattanasin, 93 F.3d 1559, 1564 (Fed. Cir. 1996).

FINDINGS OF FACT

Specification

1. The Specification describes mutations in the MSR1 gene, including R293X and D174Y, which indicate an increased risk of prostate cancer in a subject as compared to subjects without the mutation (Spec. ¶¶10, 11, 14).
2. The Specification describes a nonsense mutation, R293X, in Exon 6 of the MSR1 gene (Spec. ¶58). The mutation was observed in four different families, all of whom were Caucasian (*id.*).
3. "The mutation segregates well, although not completely, with prostate cancer in these nuclear families" (Spec. ¶59).
4. The frequency of the R293X mutation was determined in non-hereditary prostate cancer patients ("sporadic") and unaffected men (Spec. ¶65). The mutation "was only found in Caucasian subjects and was more often observed in cases (n=3, 1.3%) than in controls (n=1, 0.6%)" (*id.*).
5. The Specification states that "these results suggest that [the R293X mutation is] low frequency and potentially high penetrance" (Spec. ¶65).
6. The Specification also states that the difference in mutation carrier rates suggests that "the mutation carriers have an increased risk for prostate pathology" (Spec. ¶67).
7. The Specification describes a missense mutation, D174Y, in Exon 4 of the MSR1 gene (Spec. ¶60). The mutation was observed in four African American families (*id.*).
8. The mutation "segregates well, but not completely with prostate cancer in these families" (Spec. ¶60).

9. The D174Y mutation was found more often in prostate cancer cases (n=3, 7%) than in unaffected controls (n=2, 1.8%) (Spec. ¶65).
10. The Specification states that "these results suggest that [the D174Y mutation is] low frequency and potentially high penetrance" (Spec. ¶65).
11. The D174Y mutation appeared more often in African Americans and the R293X mutation more often in Caucasians (Spec. ¶66).

Sun publication[3]

12. Sun describes a meta-analysis of the association of mutations in the MSR1 gene and prostate cancer risk (Sun, at 728). The meta-analysis included a large collection of data from previously published individual studies (*id.* at 729, first column), including those described in the Hope, Seppala, and Lindmark publications (*id.* at 737).
13. "Significant differences were observed for the genotype frequency of R293X . . . between sporadic prostate cancer patients and controls" (Sun, at 730, first column).
14. "When the meta-analysis for R293X was performed by excluding the initial report, [Sun] did not observe evidence of a significant association" (Sun, at 730, second column).
15. "A significantly increased risk was observed in D174Y carriers when a fixed effect was assumed" (Sun, at 730, second column).
16. When the initial report was excluded, Sun "did not observe evidence of a significant association" (Sun, at 730, second column).

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[3] Sun et al., "Meta-analysis of Association of Rare Mutations and Common Sequence Variants in the *MSR1* Gene and Prostate Cancer Risk", *The Prostate*, 66:728-737 (2006).

17.

> Overall, there was evidence for association between sporadic prostate cancer risk and R293X among white men, and evidence for . . . D174Y . . . among black men. However, other pieces of evidence do not corroborate our overall findings: results from meta analysis of [R293X and D174Y] were not statistically significant when the initial report was excluded . . . ; there is a lack of evidence supporting an association between R293X and hereditary/familial prostate cancer.

(Sun, at 735, second column.)

18. After discussing several of the published studies on the R293X mutation, including several reporting no association with prostate cancer, Sun concludes:

> Taken together, our results suggest that R293X is unlikely to be a highly penetrant variant that leads to familial and hereditary prostate cancer; however, it may confer a moderate risk to sporadic prostate cancer.

(Sun, at 736, second column.)

19. For the D174Y mutation, Sun states that "there is reasonable evidence to suggest that the D174Y mutation may confer a moderate risk to prostate cancer among black men" (Sun, at 736, second column).

ANALYSIS

The dispute in this appeal involves the question of whether the Specification teaches how to use the claimed method of screening a subject for increased risk of prostate cancer comprising detecting the presence of the R293X and D174Y mutations in the MSR1 gene.

After reviewing the evidence in the Specification describing the relationship between the R293X and D174Y mutations and prostate cancer,

the Examiner concludes that it "has not [been] shown that the correlation between the claimed mutations and the risk of both sporadic and hereditary prostate cancers is significant in all populations" (Ans. 11). The Examiner contends that post-filing date published references – Hope, Seppala, and Lindmark – show "that there is no statistically significant association between mutations in MSR1 and the risk of prostate cancer" (*id.* at 9).

The Examiner also cites pre-filing date publications which provide evidence of the unpredictability in the relationship between gene mutations and disease (*id.* at 6-8). None of these pre-filing date publications describe the MSR1 gene or MSR1 gene mutations, but rather generically discuss the field.

Based on the evidence, the Examiner concludes:

> In order for one skilled in the art to use the claimed method to screen a subject for increase risk of prostate cancer, the claimed MSR1 mutations must correlate to the risk of prostate cancer, and such correlation must be statistically significant. Without such correlation, one skilled in the art would not be able to screen a subject for the risk of the prostate cancer.

(Ans. 12.)

We have carefully considered the evidence proffered by the Examiner, but are not persuaded that the Examiner met the burden of establishing a reasonable basis to question the enablement provided for the claimed invention.

The Specification provides evidence that the R293X and D174Y mutations occurred in several families with familial or hereditary prostate cancer (Finding of Fact ("FF") 2, 3, 7, & 8). The mutation was not always associated with prostate cancer (FF3, 8). However, 100% correspondence is not necessary to meet the limitation of claim 1 of an "increased risk of

prostate cancer." As we interpret the claim, an "increased risk" would be understood to mean an increased possibility or probability of getting prostate cancer when the mutation is present. That limitation is met by the disclosure that the R293X and D174Y mutations segregate "well", but not "completely" with prostate cancer in the identified families (FF3, 8) because it indicates an increased probability of getting cancer.

In addition to the occurrence of the mutations in hereditary prostate cancers, the Specification also describes their occurrence in sporadic cases. The Specification reports that the R293X and D174Y mutations occur at a low frequency in the population but that each is associated with an increased risk of prostate cancer (FF4-6, 9, & 10).

The Examiner does not appear to question the data in the Specification, but contends that the enablement problem stems from the fact that the elevated risk is not present in all populations (Ans. 11). The Examiner's complaint is apparently based on the Specification disclosure that the hereditary R293X mutation was found in Caucasians, the hereditary D174Y mutation in African Americans, and the same racial pattern for the sporadic R293X and D174Y mutations (FF11).

"[I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976)." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Thus, while it may be true that the Specification's teachings indicate that the elevated cancer risk for the R293X and D174Y mutations might be correlated with a subject's race, there is still sufficient evidence that the generic claim for

detecting increased prostate cancer risk is enabled by the Specification. It is not a function of the claims to specifically exclude possible inoperative embodiments. *Atlas Powder Company v. E.I. Du Pont De Nemours & Company*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

The Examiner also contends that the Specification does not enable the claimed method because there is not a "significant correlation" between prostate cancer risk and the R293X and D174Y mutations (Ans. 12). The Examiner's conclusion is based on post-filing publications which determined the incidence of R293X and D174Y mutations, and concluded they were not associated with a cancer risk (*id.* at 9).

It is unnecessary for Appellants to prove with 100% certainty that a correlation exists between the R293X and D174Y mutations and an increased prostate cancer risk. It is sufficient that that the evidence is "reasonably indicative" that a correlation is present. As the Federal Circuit put it in *Fujikawa v. Wattanasin*, 93 F.3d at 1564, "there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior."

There is no reason to treat a gene mutation, whose activity is to elevate prostate cancer risk, differently from a compound having a useful pharmacological activity. Each possesses a desired biological and medically relevant activity. Thus, the question boils down to whether a person of skill in the art would have been convinced that the R293X and D174Y mutations increase the risk of prostate cancer as required by claim 1. *Fujikawa v. Wattanasin*, 93 F.3d at 1564.

The Sun publication analyzed several independent published studies involving the association of MSR1 and prostate cancer, including the Seppala, Hope, and Lindmark papers cited in the Examiner's Answer (FF12). Despite acknowledging that not all the studies supported an elevated prostate cancer risk with the R293X and D174Y mutations (FF14, 16, 17), Sun went on to conclude that R293X "may confer a moderate risk to sporadic prostate cancer" (FF18) and that "there is reasonable evidence to suggest that the D174Y mutation may confer a moderate risk to prostate cancer among black men" (FF19). As it is unchallenged that the Sun publication was authored by persons of ordinary skill in the pertinent field of invention, we consider these statements as evidence that such persons were convinced "to a reasonable probability" that the R293X and D174Y gene mutations are associated with an increased risk of prostate cancer as recited in claim 1.

The Examiner admits that Sun teaches "at best that there is a correlation of R293X and risk of sporadic prostate cancer in white man, and a correlation of D174Y and risk of sporadic prostate cancer in black man" (Ans. 13-14). The Examiner nonetheless rejects this evidence because the elevated risk is not in all populations. As explained above, it is unnecessary for the claims to exclude all inoperative embodiments as long as the generic invention is enabled. Here, there is ample evidence that the Specification teaches how to use the recited mutations to determine prostate cancer risk (FF2-10).

CONCLUSION OF LAW

The Examiner did not establish a reasonable basis to question the enablement for the full scope of the claimed method for screening a subject for increased risk of prostate cancer. We reverse the rejection of claims 1 and 5-8.

REVERSED

Ssc:

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